DETAILED ACTION

Status of the Application

1. Applicant's response filed on April 13, 2011 is acknowledged. Claims 14, 16, 18-23, 25, 27-31, 52-55, 62, 63, 71, and 73 are currently pending. In the response, Applicant amended claims 14, 16, 23, 25, 27, 28, 30, 31, and 71 and canceled claims 69 and 72.

The following include new grounds of rejection necessitated in part by Applicant's amendments to the claims. Any previously made rejections or objections not reiterated below have been withdrawn. Applicant's arguments filed on April 13, 2011 have been fully considered and are discussed in the "Response to Arguments" section. Since the not all of the new grounds of rejection were necessitated by Applicant's amendment, this Office Action is **NON-FINAL**.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In this case, the disclosure of the prior-filed application, Provisional Application No. 60/504,087, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for all of the pending claims in the instant application. The '087 provisional application does not provide adequate support for the requirement in all of the instant claims to determine the ratio of HoxB13 and IL17BR RNA expression levels. Also, as discussed in greater detail below, neither of the prior-filed applications (*i.e.*, non-provisional Application Serial No. 10/727,100 and Provisional Application No. 60/504,087) provides adequate support for using the average HoxB13:IL17BR mRNA expression level ratio determined from HoxB13 and IL17BR mRNA expression levels in ER+ breast cancer cells obtained from human breast cancer patients that respond to treatment with an antiestrogen agent and from human breast cancer patients that do not respond to treatment with the antiestrogen agent to predict a patient outcome, specifically responsiveness to anti-estrogen therapy or cancer recurrence. Further, neither the '100 application nor the '087 application provides support for letrozole, which is optional for the methods of claims 14, 18-23, 27-31, 52-55, 62, and 63 and required for the methods of claims 71 and 73. Accordingly, benefit of the prior-filed '087 and '100 applications has not been granted, and the filing date of the instant application, (**February 6, 2004**) has been used for prior art purposes.

Claim Objections

3. Claim 73 is objected to because its status identifier is incorrect.

Claim Rejections - 35 USC § 112, 1st paragraph (New Matter)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16, 18-23, 25, 27-31, 52-55, 62, 63, 71, and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

MPEP 2163.03 states, "An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed." *In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989). MPEP 2163.05 states, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement." *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

These claims are drawn to methods that comprise determining the ratio of HoxB13:IL17BR mRNA expression in a sample of estrogen receptor-positive (ER+) breast cancer cells obtained from a human patient and comparing the ratio to a mean ratio of HoxB13 to IL17BR mRNA expression levels determined from a cohort of ER+ breast cancer patients known to be responders or non-responders to an anti-estrogen agent, wherein a HoxB13:IL17BR mRNA expression level ratio that is higher than the mean ratio is indicative of an increased risk of

cancer recurrence if the patient is treated with an anti-estrogen agent, specifically tamoxifen or letrozole.

Applicant has stated that the recitations in the claims concerning comparison to a mean ratio find support throughout the application as filed and, in particular, at Figures 3, 6, and 7 and Examples 3 & 4 of Application Serial No. 10/727,100, to which the instant application claims priority and which has been expressly incorporated by reference.

The original disclosure, including the disclosure of the incorporated '100 application, has been carefully reviewed, but it does not appear to provide adequate support for the claimed methods in which a mean HoxB13:IL17BR mRNA expression level ratio is used as a comparison point for HoxB13:IL17BR mRNA expression level ratios determined from a ER+ breast cancer cell sample obtained from a human patient. The instant application and the incorporated '100 application appear to provide proper support for the following (see Figure 2a-2d and Examples 3-4 of the instant application; see also Examples 3 & 4 and Figures 3, 6, and 7 of the '100 application, which were cited by Applicant as providing support for the claimed recitations): (i) measuring HoxB13 & IL17BR mRNA expression levels in a sample of ER+ breast cancer cells obtained from a human patient and determining a ratio of HoxB13:IL17BR mRNA expression levels in said sample, and (ii) comparing the mRNA expression level ratio determined in step (i) to a threshold HoxB13:IL17BR mRNA expression level ratio that accurately classifies the patient as likely or unlikely to respond to tamoxifen treatment. It is noted that, as discussed by Applicant at pages 8-9 of the response, the zero point on the Y-axis of Figure 7 of the '100 application represents the mean ratio of HoxB13:IL17BR mRNA expression levels. However, it does not appear from the disclosure that the mean ratio was used as a

comparison point as required by the claims. Rather, based on the disclosure in Example 4 of the '100 application, it would appear that a value other than the zero point of the Y-axis of Figure 7 was used as the comparison point (see page 72 and Figure 7, where a value of -0.22 or 0.22 was used as the point of comparison). There is also no discussion of the mean HoxB13:IL17BR mRNA expression level ratio in either the instant application or the incorporated '100 application or using the mean expression level ratio as a comparison point for classifying test samples. As a result, the original disclosure does not appear to provide adequate support for the claimed methods in which the mean ratio is used to classify patients as likely or unlikely to respond to tamoxifen treatment, and, accordingly, claims 14, 16, 18-23, 25, 27-31, 52-55, 62, 63, 71, and 73 have been rejected under 35 U.S.C. 112, first paragraph for incorporating new matter.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 14, 16, 18, 19, 21-23, 25, 27, 28, 30, 31, 52-55, 62, and 63 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 7,504,214 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the methods recited in claims 1-43 of the '214 patent recite all of the limitations of the instant claims 14, 16, 18-23, 25, 27-31, 52-55, 62, and 63. Thus, the instant claims 14, 16, 18, 19, 21-23, 25, 27, 29, 30, 31, 52-55, 62, and 63 are not patentably distinct from claims 1-43 of the '214 patent.

7. Claims 20 and 29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 7,504,214 B2 in view of Gibson et al. (Genome Research (1996) 6: 995-1001; newly cited).

The claims of the '214 patent recite qPCR rather than real-time PCR as required by the instant claims 20 and 29. However, the ordinary artisan would have been motivated to conduct the qPCR step using any known qPCR method, such as real-time PCR, since Gibson taught that the disclosed real-time qRT-PCR method, which utilizes comparative Ct values, is faster and less labor-intensive than conventional qPCR methods (page 998, column 2 – page 999, column 1). Thus, the instant claims 20 and 29 are not patentably distinct from claims 1-43 of the '214 patent in view of Gibson.

Response to Arguments

8. Applicant's arguments filed on April 13, 2011 have been fully considered.

Objection to claims 14 and 23

Applicant argues that the claim amendments have obviated the previously made objection concerning spelling out of the HoxB13 and IL17BR gene names in claims 14 and 23 (page 7). Applicant also argues that no change to the preamble of claim 14 is necessary (page 8). Applicant's arguments were persuasive, and, accordingly, the objections have been withdrawn.

Rejection of claims 25, 27-31, 69, and 71 under 35 U.S.C. 112, second paragraph

Applicant argues that the rejection is moot in view of the claim amendments (page 8). This argument was persuasive, and accordingly, the rejection has been withdrawn.

Rejection of claims 14, 16, 18-23, 25, 27-31, 52-55, 62, 63, 69, and 71-73 under 35 U.S.C. 112, first paragraph (new matter)

Applicant argues that, since the value "0" on the vertical axis of Figure 7 of the prior-filed '100 application, which was incorporated by reference into the instant application, indicates the

mean or average ratio of expression levels, the disclosed methods inherently comprise comparison to this average value regardless of whether or not a cutoff point of -0.22 was also used (pages 8-9).

This argument was not persuasive, because the claimed methods require using a comparison to the mean expression level ratio to predict the likelihood of a particular outcome, specifically cancer recurrence or responsiveness to treatment with tamoxifen or letrozole. There is no indication that the mean expression ratio was used for this comparison, since, as discussed in the rejection, the disclosure only describes using the cutoff value in this way. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Rejection of claims 14, 16, 18-23, 25, 27-31, 52-55, 62, 63, 69, and 72 under 35 U.S.C. 112, first paragraph (Scope of Enablement)

Applicant argues that the rejection is moot in view of the claim amendments (page 9). This argument was persuasive, and, accordingly, the rejection has been withdrawn.

Conclusion

9. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637